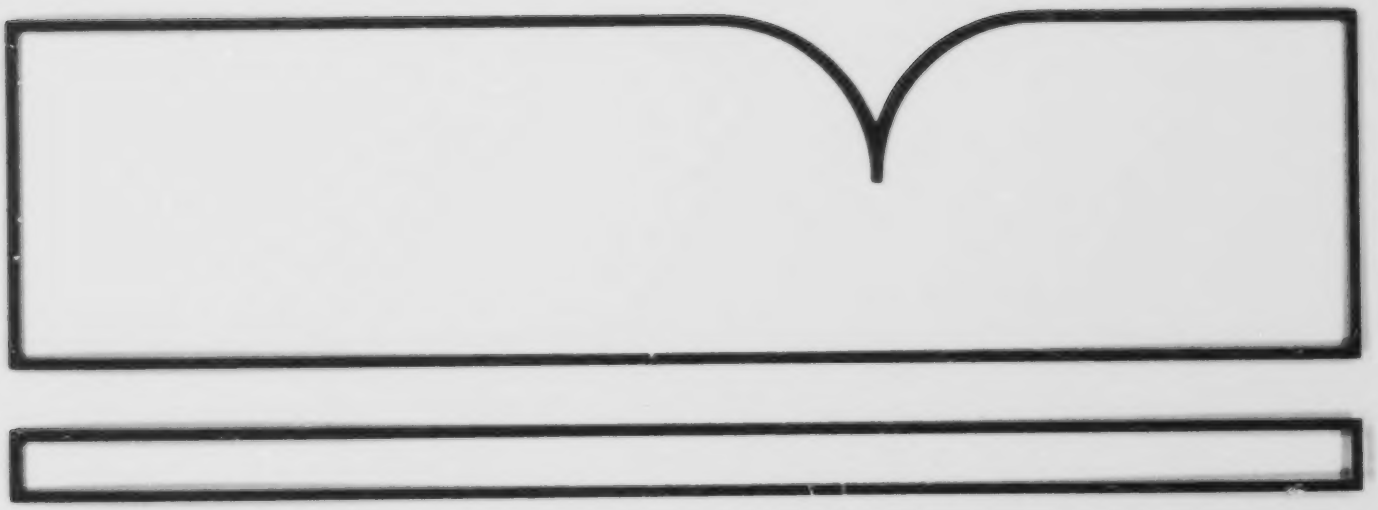
PB88-220751

Health and Environmental Effects Profile for Diethylforamide

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jun 86



U.S. Department of Commerce
National Technical Information Service
NTIS

PB86-220751

EPA/600/X-86/158
June 1986

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR DIETHYLFORMAMIDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA/600/X-86/158	2.
3. RECIPIENT'S ACCESSION NO. PB88-220751/AS	
4. TITLE AND SUBTITLE: Health and Environmental Effects Profile for Diethylformamide	5. REPORT DATE: June 1986
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS: Environmental Criteria and Assessment Office, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE: EPA/600/22
15. SUPPLEMENTARY NOTES	

16. ABSTRACT

The Health and Environmental Effects Profile for Diethylformamide was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Diethylformamide has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for diethylformamide is 0.011 mg/kg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group

18. DISTRIBUTION STATEMENT: Public	19. SECURITY CLASS (This Report): Unclassified	21. NO. OF PAGES: 40
	20. SECURITY CLASS (This page): Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constit- uents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

EXECUTIVE SUMMARY

Diethylformamide does not appear to be manufactured in the United States on a commercial scale; however, its use in rubber manufacture has been cited (Dunlap et al., 1976). It has been detected in effluents from latex manufacturing plants (Shackelford and Keith, 1976) and in landfill leachates and groundwater (Dunlap et al., 1976; Shackelford and Keith, 1976).

Experimental environmental fate data have not been generated with respect to diethylformamide. Estimation methods predict that diethylformamide will not bioaccumulate, hydrolyze, volatilize or adsorb significantly in the aquatic environment. Leaching of diethylformamide in moist soils can be expected to occur. Removal of the compound from the atmosphere through rainfall is potentially important.

Pertinent data regarding the pharmacokinetics and metabolism of diethylformamide in mammals could not be located in the available literature as cited in the Appendix.

Treatment of rats by gavage with diethylformamide at 546 µg/day, 5 days/week (1.11 mg/kg/day, assuming an average rat weight of 0.35 kg) for up to 73 weeks resulted in the appearance of a lymphosarcoma in 1/27 rats, which was observed after 92 days of treatment (Argus et al., 1965). A lymphosarcoma also developed in 1/9 untreated controls after 399 days of observation. While a weak treatment-related carcinogenic response was not ruled out (Argus et al., 1965), it is not possible to draw a conclusion regarding the carcinogenicity of diethylformamide from these data.

Pertinent information regarding the mutagenicity, teratogenicity and other reproductive effects of diethyl formamide could not be located in the available literature as cited in the Appendix. No non-neoplastic effects were observed in the carcinogenicity study; however, information regarding the toxic effects of repeated exposure to diethylformamide was available from a study in which the chemical was administered intraperitoneally to rats. At an intraperitoneal dose of 60 mg/kg/day, 5 days/week for 7 weeks, rats had decreased body weight gain and clinical evidence of immunotoxic and antidiuretic effects (Pham et al., 1971; Azum-Gelade, 1974).

The intraperitoneal LD_{50} of diethylformamide was 1500 mg/kg for rats and 1900 for mice (Pham et al., 1971). Death of 50% of the rats and mice occurred within 15 and 7 days, respectively at intraperitoneal doses of 1200 and 1300 mg/kg, respectively. Effects of acute intraperitoneal intoxication included decreased motor activity, nervousness, tonic and chronic convulsions, injection site hepatic lesions of rats and mice, prolonged hexabarbital-, chloral- and urethane-sleeping times of rats (Pham et al., 1971; 1972). Diethylformamide stimulated the respiratory and cardiovascular systems of anesthetized dogs at an intravenous dose of 500 mg/kg (Azum-Gelade, 1974). Dose-related depression of the contractile force of the perfused hearts of rabbits and the coronary circulation occurred with $\geq$60 mg/heart.

Intraperitoneal pretreatment of rats with diethylformamide inhibited the covalent binding of dimethylnitrosamine to liver protein (Mirvish and Sidiansky, 1971). In vitro, diethylformamide caused hemolysis of human erythrocytes (Cadwallader and Phillips, 1969) and denatured ovalbumin (Argus et al., 1966).

A provisional ADI of 0.77 mg/day for a 70 kg man was calculated from the chronic oral NOEL in rats of 1.11 mg/kg/day in the study a Argus et al. (1965) using an uncertainty factor of 100. It was noted that the ADI may be too conservative because the threshold for effects may be much higher than the NOEL. The ADI should be regarded as provisional until the possibility of a carcinogenic effect can be ruled out.

Data were not sufficient to derive an RQ based on chronic toxicity. Diethylformamide was placed in IARC Group 3 and CAG Group D as a chemical that cannot be classified as to its carcinogenic potential for humans.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	2
1.5.	SUMMARY	2
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	3
2.1.	WATER	3
2.1.1.	Hydrolysis	3
2.1.2.	Oxidation	3
2.1.3.	Photolysis	3
2.1.4.	Microbial Degradation	3
2.1.5.	Volatilization	3
2.1.6.	Adsorption	4
2.1.7.	Bioaccumulation	4
2.2.	AIR	4
2.2.1.	Chemical Removal Processes	4
2.2.2.	Physical Removal Processes	4
2.3.	SOIL	4
2.3.1.	Microbial and Chemical Degradation	4
2.3.2.	Leaching	4
2.3.3.	Volatilization	5
2.4.	SUMMARY	5
3.	EXPOSURE	6
3.1.	WATER	6
3.2.	FOOD	6
3.3.	INHALATION	6
3.4.	DERMAL	6
3.5.	SUMMARY	6
4.	PHARMACOKINETCS	7

TABLE OF CONTENTS (cont.)

		Page
5.	EFFECTS	8
5.1.	CARCINOGENICITY	8
5.2.	MUTAGENICITY	10
5.3.	TERATOGENICITY	10
5.4.	OTHER REPRODUCTIVE EFFECTS	10
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	10
5.6.	OTHER RELEVANT INFORMATION	11
5.7.	SUMMARY	14
6.	AQUATIC TOXICITY	16
7.	EXISTING GUIDELINES AND STANDARDS	17
7.1.	HUMAN	17
7.2.	AQUATIC	17
8.	RISK ASSESSMENT	18
9.	REPORTABLE QUANTITIES	20
9.1.	REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY	20
9.2.	WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY	20
10.	REFERENCES	23
APPENDIX:	LITERATURE SEARCHED	27

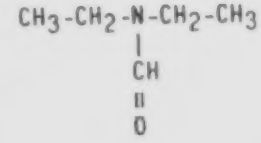
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical Abstract Service
i.p.	Intraperitoneal
i.v.	Intravenous
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Diethylformamide is the common chemical name, but this compound is also known by the synonyms N,N-diethylformamide and formyldiethylamine. The structure, molecular weight empirical formula and CAS Registry number for diethylformamide are as follows:



Molecular weight: 101.17

Empirical formula: $C_5H_{11}NO$

CAS Registry number: 617-84-5

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Diethylformamide is a liquid at room temperatures; selected physical properties are listed below:

Boiling point:	177-8°C	Weast, 1985
Melting point:	no data	
Specific gravity (19°C):	0.9080	Weast, 1985
Refractive index (25°C):	1 4321	Weast, 1985
Water solubility:	miscible	Weast, 1985
Vapor pressure mm Hg: at 30°C at 20°C at 25°C	 2.0 0.82 1.21	Gopal and Rizvi, 1968
Log K_{ow}:	0.20 (calculated)	U.S. EPA, 1985

In addition to water, diethylformamide is soluble in alcohol, ether, acetone and benzene (Weast, 1985).

1.3. PRODUCTION DATA

Diethylformamide is not cited as a commercially manufactured compound in the United States (SRI, 1985; USITC, 1984). The U.S. EPA TSCA Production File for 1977 lists Eastman Kodak (Rochester, NY) and Fike Chemicals (Nitro, WV) as capable of manufacturing diethylformamide; however, neither company produced any diethylformamide in 1977.

Diethylformamide can be prepared by the reaction of diethylamine with carbon monoxide in the presence of propanol (Bankowski et al., 1959).

1.4. USE DATA

Diethylformamide is used in rubber manufacture (Dunlap et al., 1976); its specific use application was not available. The commercially important and similarly structured dimethylformamide is a widely used and powerful solvent (Eberling, 1980).

1.5. SUMMARY

Diethylformamide does not appear to be manufactured on a commercial scale in the United States. Its use in rubber manufacture has been reported. Water solubility and vapor pressure data are available for the estimation of environmental fate processes. The log K_{ow} has been calculated to be 0.20 based on the structure of diethylformamide (U.S. EPA, 1985).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. **Hydrolysis.** Experimental hydrolysis rate data regarding diethylformamide were not found. Aqueous solutions of dimethylformamide have little tendency to hydrolyze at neutral pH (Eberling, 1980). In addition, most amides have a hydrolytic half-life greater than a year at pH7 and 25°C (Neely, 1985). This suggests that diethylformamide will not undergo rapid environmental hydrolysis.

2.1.2. **Oxidation.** Data regarding the oxidation of diethylformamide in the aquatic environment could not be located in the available literature as cited in the Appendix.

2.1.3. **Photolysis.** Data regarding the photolysis of diethylformamide in the aquatic environment could not be located in the available literature as cited in the Appendix.

2.1.4. **Microbial Degradation.** Data regarding the microbial degradation of diethylformamide in the aquatic environment could not be located in the available literature as cited in the Appendix.

2.1.5. **Volatilization.** Experimental data were not found; however, Henry's Law Constant can be estimated. Estimation using the activity coefficient group contribution method of Hine and Mookerjee (1975) predicts an air-to-water ratio at 25°C to be 1.1×10^{-6}, which is equivalent to a Henry's Law Constant of 2.64×10^{-8} atm-m³/mole. Henry's Constant can also be calculated from the vapor pressure of diethylformamide (1.21 mm Hg at 25°C) and the water solubility (assumed to be 10^6 ppm for a completely miscible compound) to be $\sim 1.6 \times 10^{-7}$ atm-m³/mole. Both estimations of Henry's Constant indicate that diethylformamide will not volatilize from the aquatic environment to any significant extent (Lyman et al., 1982).

2.1.6. **Adsorption.** The complete water solubility and log K_{ow} value (0.20) of diethylformamide suggest that adsorption to particulate organic matter and sediment in water will not be environmentally important.

2.1.7. **Bioaccumulation.** Experimental data are not available; however, the complete water solubility and log K_{ow} value (0.20) indicate that bioconcentration in aquatic organisms is not expected to be significant.

2.2. AIR

2.2.1. **Chemical Removal Processes.** Data regarding the chemical removal of diethylformamide from the atmosphere could not be located in the available literature as cited in the Appendix.

2.2.2. **Physical Removal Processes.** The complete water solubility of diethylformamide suggests that removal by dissolution into clouds and subsequent rainfall or by the wash-out effect of rainfall has potential importance. As noted in Section 2.1.5., the estimated Henry's Law Constants for diethylformamide predict little volatilization from water.

2.3. SOIL

2.3.1. **Microbial and Chemical Degradation.** Pertinent data regarding these fate mechanisms could not be located in the available literature as cited in the Appendix.

2.3.2. **Leaching.** The complete water solubility and log K_{ow} value (0.20) suggest that leaching into soil and, potentially into groundwater, is possible. The molecular topology and quantitative structure-activity relationship analysis method of Sabljic (1984) predicts that diethylformamide will have a soil sorption coefficient of about 195, which indicates a medium mobility in soil.

2.3.3. **Volatilization.** The vapor pressure of diethylformamide at -20° (0.82 mm Hg) suggests that evaporation from dry soil surfaces is likely to significant. However, in moist soils, the leaching effect of water and the very low estimated Henry's Law Constant for diethylformamide indicate little importance for evaporation.

2.4. SUMMARY

Experimental data could not be located in the available literature as cited in the Appendix for any of the environmental fate or transport processes with respect to diethylformamide. Therefore, prediction of its environmental fate must be done by estimation methods. Aquatic hydrolysis, volatilization, adsorption and bioaccumulation are predicted to be unimportant. Removal of diethylformamide from the atmosphere through dissolution/rainfall has potential importance. Leaching of diethylformamide in moist soils can be expected to occur.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET Data Base contains no observations for diethylformamide.

Dunlap et al. (1976) identified diethylformamide in leachate collected from test wells drilled near a landfill disposal site in Norman, Oklahoma; concentrations were not reported. Shackelford and Keith (1976) have reported the detection of diethylformamide in effluents from latex manufacturing plants and from a landfill leachate; concentrations or locations were not reported. Shackelford and Keith (1976) also reported that diethylformamide was identified in groundwater from Oklahoma City, OK (no concentrations given) and from an unidentified well.

3.2. FOOD

Pertinent data pertaining to the detection of diethylformamide in foods could not be located in the available literature as cited in the Appendix.

3.3. INHALATION

Reports considering the detection of diethylformamide in ambient air could not be located in the available literature as cited in the Appendix. Grosjean et al. (1978) have reported that irradiation of diethylnitrosamine in a smog chamber produced diethylformamide as one of several products.

3.4. DERMAL

Data pertaining to the dermal monitoring of diethylformamide could not be located in the available literature as cited in the Appendix.

3.5. SUMMARY

Diethylformamide has not been detected in food or in ambient air. It has been identified in latex manufacturing plant effluents, in landfill leachate, and in groundwater.

4. PHARMACOKINETICS

Pertinent data regarding the absorption distribution, metabolism and excretion of diethylformamide could not be located in the available literature as cited in the Appendix.

5. EFFECTS

5.1. CARCINOGENICITY

Information regarding the carcinogenicity of diethylformamide is limited. Argus et al. (1965) administered the compound in water by gavage to 27 adult (150-200 g) male Wistar rats at a dosage of 546 µg/day, 5 days/week for 73 weeks. If the average weight of the rats over the course of the study is assumed to be 0.35 kg, the dosage can be expressed as 1.56 mg/kg/day, 5 days/week. A group of 9 untreated rats served as controls; there was no vehicle control group. Necropsy and comprehensive histological examination were performed on all rats that died during the experiment or that were killed at the end of the experiment. Mortality data was not reported.

Weekly weighing of the rats indicated that they gained weight normally and weighed 500-580 g at the end of the experiment; weight gain per week was not reported. As seen from Table 5-1, lymphosarcomas developed in 1/27 treated rats and 1/9 control rats. The tumor was observed in the treated rat after 92 days of treatment with a total dose of 36 mg or 0.39 mg/day. Without specific weight gain data, it is difficult to calculate a dose in mg/kg/day for this rat. For the control rat, the lymphosarcoma was observed after 399 days of the experiment.

The possibility that the early appearance of the lymphosarcoma in the treated rat was compound-related could not be excluded; therefore, the carcinogenicity of diethylformamide was being re-investigated in the laboratory (Argus et al., 1965). No report of a subsequent study, however, was located in the available literature, and diethylformamide is not scheduled for testing by the National Toxicology Program (NTP, 1985). Therefore, it is not possible to draw a conclusion regarding the carcinogenicity of diethylformamide.

TABLE 5-1

Incidence of Tumors in Male Wistar Rats Treated by Gavage with Diethylformamide[a]

Dose[b] (mg/kg/day)	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle	Target Organ	Tumor Type	Tumor Incidence
1.56, 5 days/week	73 weeks	73 weeks	NR	distilled water	lymphoid tissue	lymphosarcoma	1/27[c]
0	NA	73 weeks	NA	NA	lymphoid tissue	lymphosarcoma	1/9[d]

QUALITY OF EVIDENCE

Strengths of Study: The chemical was administered by a relevant route for a significant portion of the lifespan. Comprehensive histological examination was performed on all rats that died or were killed at the end of the study.

Weakness of Study: Only one dose was administered to one sex of one species. Group sizes were small, especially the control group, which received no treatment (there was no vehicle control group).

Overall Adequacy: Inadequate

[a]Source: Argus et al., 1965

[b]The dose was reported as 546 µg/day, 5 days/week. The dose in mg/kg/day was calculated by dividing the reported dose by an assumed average body weight of rats of 0.35 kg.

[c]The tumor developed within 92 days of treatment

[d]The tumor developed within 399 days of the start of the experiment

NA = Not applicable; NR = not reported

5.2. MUTAGENICITY

Pertinent data regarding the mutagenicity of diethylformamide could not be located in the available literature as cited in the Appendix.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of diethylformamide could not be located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of diethylformamide could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The only available study of chronic exposure of animals to diethylformamide is the previously described carcinogenicity study (see Section 5.1.) conducted by Argus et al. (1965). In this study rats were treated by gavage with 546 µg/day 5 days/week (1.56 mg/kg/day, 5 days/week, assuming an average weight of 0.35 kg for rats), for 73 weeks. The rats were weighed weekly, and necropsy and comprehensive histological examination were performed on all the rats that died or were killed at the end of the study. No non-neoplastic effects were observed.

Information concerning the effects of repeated exposure to diethylformamide were available only from a subchronic study in which the animals were treated intraperitoneally. Pham et al. (1971) treated a group of 20 male Wistar rats by i.p. injection with diethylformamide in saline at 60 mg/kg/day, 5 days/week for ~7 weeks (36 injections, total). Two additional groups of 20 rats each served as vehicle and untreated controls. The rats were observed for behavorial changes and body weight gain. Measurements of hematologic, clinical chemistry and urinalysis parameters were made after 15 and 36 injections. The rats were killed after the last treatment, and

necropsy and histological examination of heart, spleen, kidney, adrenals, liver, lung, pancreas, thyroid, testes and abdominal aorta were performed.

There were no outward signs of toxicity; however, decreased body weight gain was observed in the treated rats. It is not clear from the report if the decrease was significantly different from controls. There were no deaths. No effects on erythrocyte count, hemoglobin concentration or hematocrit were observed, but the leucocyte count was increased above control (not otherwise specified) by ~24% after 15 injections and ~39% after 36 injections. The only significant changes in serum proteins were 33 and 9% decreases in the content of gamma globulins after 15 and 36 injections, respectively. Serum calcium levels were increased during exposure while serum sodium and potassium levels were increased after 15 injections and decreased after 36 injections. An appreciable decline in the urinary levels of calcium, sodium and potassium was measured after 36 injections. No treatment-related histopathologic lesions were observed.

In summary, no effects of repeated exposure to diethylformamide were observed in rats treated by gavage with ~1.56 mg/kg/day, 5 days/week for 73 weeks (Argus et al., 1965). Repeated i.p. dosing of rats with 60 mg/kg/day, 5 days/week for 7 weeks, however, resulted in decreased body weight gain, a possible immunotoxic effect (decreased serum δ-globulin) and an anti-diuretic effect (decreased urinary excretion of calcium, sodium and potassium) (Pham et al., 1971).

5.6. OTHER RELEVANT INFORMATION

The "immediate" and delayed acute LD_{50}s of intraperitoneally or intravenously administered diethylformamide were determined for Wistar rats and Swiss mice (Pham et al., 1971; Azum-Gelade, 1974). The immediate LD_{50}s were 1500 mg/kg (i.p.) and 1200 mg/kg (i.v.) for rats and 1000 mg/kg (i.p.)

and 2000 mg/kg (i.v.) for mice. For rats, the delayed LD_{50}s were 1200 mg/kg with 50% mortality at 15 days for i.p. injection and 24 hours for i.v. dosing. For mice, 50% mortality occurred within 7 days of i.p. dosing with 1300 mg/kg and within 24 hours of i.v. dosing with 3100 mg/kg. Therefore, for rats, i.v. administration of diethylformamide resulted in greater toxicity than did i.p. treatment; while in mice, the i.p. administration resulted in greater toxicity than did i.v. dosing, at least in the immediate LD_{50} determination.

The surviving animals in these experiments were observed for 30 days. Necropsy and histological examination of major organs were performed on all animals that died or were killed after 30 days of observation. In animals treated with the highest dose that produced no mortality in 30 days [<500 mg/kg (i.p.) and 2000 mg/kg (i.v.) for mice], the animals had perceptibly decreased motor activity, characterized by immobility, prostration and reduced pain and righting reflexes. They regained activity 6 hours later, but remained sluggish and had rough hair. At 24 hours after treatment they displayed nervousness. At higher doses, the state of lethargy was followed by a period of nervousness and convulsions at 3 hours. Tonic and clonic convulsions appeared 5-10 minutes after dosing at or near the LD_{100} [2400 mg/kg (i.p.) and 1340 mg/kg (i.v.) for rats; 3200 mg/kg (i.p.) and 4000 mg/kg (i.v.) for mice]. Histological examination revealed necrosis of the liver and polynuclear hepatic parenchymal cells of mice treated intraperitoneally or intravenously these lesions were found near the i.p. injection site.

Intraperitoneal dosing of Wistar rats with a single dose of ~500 mg/kg diethylformamide had no effect on blood levels of GOT, GPT, lactic dehydrogenase (LDH), sorbitol dehydrogenase (SDH), acid phosphatase, cholinesterosl

or ATP (Azum-Gelade, 1974). Aldolase levels were slightly increased above control at 15 minutes after dosing, but returned to normal at 34 hours after dosing. Arylesterase activity was decreased at 24 hours.

In other experiments, Azum-Gelade (1974) found that diethylformamide had no effect on glucose production in the isolated perfused rat liver *in situ*. Diethylformamide stimulated the respiratory and cardiovascular systems of anesthetized dogs that were treated intravenously with 500 mg/kg. Diethylformamide at a dose of 60 mg depressed the contractile force of the perfused isolated rabbit heart by 15% and inhibited coronary circulation by 40%; at 100 mg cardiac contraction and coronary circulation were completely inhibited.

Intraperitoneal injection of mice with 750 mg/kg diethylformamide lengthened the hexabarbitol-, chloral- and lihethane-sleeping times (Pham et al., 1972). Pretreatment of the mice with diethylformamide had no effect on the toxicity of strychnine but prolonged the duration of pentretrazole-induced convulsions.

Pretreatment of rats intraperitoneally with diethylformamide inhibited the *in vivo* labellin of liver protains by [^{3}H]-dimethylnitrosamine, presumably by blocking the metabolism of the labeled compound to a methylating agent (Mirvish and Sidranslog, 1971).

Wepierre et al. (1966) reported that diethylformamide, used as a solvent had no effect on the absorption of eserine by the skin of anesthetized rats, as measured by the physiologic action of an *in situ* nerve-muscle preparation.

In vitro studies indicated that aqueous solutions of $\geq$0.5% diethylformamide caused complete hemolysis of human erythrocytes (Cadwallader and Phillips, 1969). Argus et al. (1966) found that an aqueous solution of 1.16 M diethylformamide resulted in a 50% denaturation of a 1% ovalbumin solution at pH 5.0 and 23-25°C.

5.7. SUMMARY

Treatment of rats by gavage with diethylforamide at 546 µg/day, 5 days/week for up to 73 weeks resulted in the appearance of a lymphosarcoma in 1/27 rats, which was observed after 92 days of treatment (Argus et al., 1965). A lymphosarcoma also developed 1/9 untreated controls after 399 days of observation. While a weak treatment-related carcinogenic response wasnot ruled out (Argus et al., 1965), it is not possible to draw a convlusion regarding the carcinogenicity of diethylformamide from these data. Pertinent information regarding the mutogenicity, teratogenicity and other reproductive effects of diethylformamide could not be located in the available literature as cited in the Appendix. No non-neoplastic effects were observed in the carcinogenicity study; however, information regarding the toxic effects of repeated exposure to diethylformamide was available from a study in which the chemical was administered intraperitoneally to rats.

At an intraperitoneal dose of 60 mg/kg/day, 5 days/week for 7 weeks, rats had decreased body weight gain and clinical evidence of immunotoxic and antidiuretic effects (Pham et al., 1971; Azum-Gelade, 1974).

The intraperitoneal LD_{50} of diethylformamide was 1500 mg/kg for rats and 1900 mg/kg for mice (Pham et al., 1971). Death of 50% of the rats and mice occurred within 15 and 7 days, respectively at intraperitoneal doses of 1200 mg/kg and 1300 mg/kg, respectively. Effects of acute intraperitoneal intoxication included decreased motor activity, nervousness, tonic and clonic convulsions, injection site hepatic lesions of rats and mice, prolonged hexabarbitol-, chloral- and urethane-sleeping times of rats (Pham et al., 1971, 1972). Diethylformamide stimulated the respiratory and cardiovascular systems of anesthetized dogs at an intravenous dose of 500

mg/kg (Azume-Gelade, 1974). Dose-related depression of the contractile force of the prefused hearts of rabbits and the coronary circulation occurred at ≥60 mg/heart.

Intraperitoneal pretreatment of rats with diethylformamide inhibited the covalent binding of dimethylnitrosamine to liver protein (Mirvish and Sidiansky, 1971). In vitro, diethylformamide caused hemolysis of human erythrocytes (Cadwallader and Phillips, 1969) and denatured ovalbumin (Argus et al., 1966).

6. AQUATIC TOXICITY

Pertinent data regarding the effects of exposure of aquatic organisms to diethylforamide could not be located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in the Appendix.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of diethylformamide could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Treatment of rats by gavage with diethylformamide at 546 µg/day, 5 days/week for up to 73 weeks resulted in the appearance of a lymphosarcoma in 1/27 rats, which was observed after 92 days of treatment (Argus et al., 1965). A lymphosarcoma also developed in 1/9 untreated controls after 399 days of observation. While a weak treatment-related carcinogenic response was not ruled out (Argus et al., 1965), it is not possible to draw a conclusion regarding the carcinogenicity of diethylformamide from these data. Pertinent information regarding the mutagenicity, teratogenicity and other reproductive effects of diethylformamide could not be located in the available literature as cited in the Appendix. No non-neoplastic effects were observed in the carcinogenicity study; however, information regarding the toxic effects of repeated exposure to diethylformamide was available from a study in which the chemical was administered intraperitoneally to rats.

Repeated intraperitoneal dosing of rats with 60 mg/kg/day, 5 days/week for 7 weeks resulted in decreased body weight gain, a possible immunotoxic effect (decreased serum gammaglobulin) and an antidiuretic effect (decreased urinary excretion of calcium, sodium and potassium) (Pham et al., 1971).

Although the study of Argus et al (1965) does not rule out a possible carcinogenic effect of diethylformamide, the chemical will be treated as a noncarcinogen for the purposes of this document. The dose administered to rats by Argus et al. (1965) was 546 µg/day, 5 days/week. If the average body weight of the rats is assumed to be 0.35 kg, the dosage can be expressed as 1.56 mg/kg/day x 5/7 (days/week) = 1.11 mg/kg/day.

This dose is a NOEL for oral exposure if the early appearance of a lymphosarcoma in one of the treated rats is considered to be unrelated to treatment. Although the threshold for toxic affects of diethylformamide following oral exposure cannot be accurately defined, it probably falls below the intraperitoneal LOAEL of 43 mg/kg/day (60 mg/kg/day x 5/7 days/ week) in the subchronic study of Pham et al. (1971). Dividing the NOEL of 1.11 mg/kg/day by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to protect the most sensitive individuals) results in a provisional ADI of 0.011 mg/kg/day or 0.77 mg/day for a 70 kg man. It should be noted that the ADI may be conservative because the threshold for toxic effects may be much high than the NOEL. Furthermore, the ADI should be regarded as provisional until the possibility of a carcinogenic effect can be ruled out.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Information regarding the effects of chronic oral or inhalation exposure to diethylformamide is limited to an early carcinogenicity study in which a group of 27 adult male Wistar rats were treated by gavage with 546 µg/day of the compound in water, 5 days/week for 73 weeks (Argus et al., 1965). Controls consisted of 9 untreated rats; there was no vehicle control group. No effects on body weight gain, mortality or gross behavior or appearance were observed. Necropsy and comprehensive histological examination of all rats that died during the experiment or that were killed at the end of the study revealed no treatment-related non-neoplastic lesions. One treated rat developed a lymphosarcoma within 92 days; one control rat developed a lymphosarcoma within 399 days. Argus et al. (1965) stated that the possibility that the early appearance of the lymphosarcoma in the treated rat was treatment-related could not be ruled out.

Because no treatment-related non-neoplastic effects were observed, it is not possible to calculate a CS and RQ for diethylformamide (Table 9-1).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Information regarding the carcinogenicity of diethylformamide is limited. Argus et al. (1965) treated a group of adult male Wistar rats by gavage with diethylformamide in water at 546 µg/day, 5 days/week for 73 weeks. Controls consisted of nine untreated rats. As seen from Table 5-1, one treated rat and one control developed a lymphosarcoma. Because the tumor appeared in the treated rat within 92 days and in the control rat at 399 days, a carcinogenic effect was not ruled out; however the data are inadequate to derive a potency factor. Argus et al. (1965) stated that the carcinogenicity of diethylformamide was being reinvestigated in their

TABLE 9-1

Diethylformamide

MINIMUM EFFECTIVE DOSE (MED) AND REPORTABLE QUANTITY (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are not sufficient for deriving an RQ.

laboratory; however, no report of a repeated study was located in the available literature. Furthermore, diethylformamide is not scheduled for testing by the National Toxicology Program (NTP, 1985).

Therefore, according to the classification scheme of IARC, diethylformamide is a Group 3 chemical (EPA Group D), that is, it cannot be classified as to its carcinogenic potetial for humans.

10. REFERENCES

Argus, M.F., J.C. Arcos and C. Hoch-Ligeti. 1965. The carcinogenic activity of protein-denaturing agents hepatocarcinogenicity of dioxane. J. Natl. Cancer Inst. 35: 949-958.

Argus, M.F., J.C. Arcos, J.H. Mathison, A. Alam and J.A. Bemis. 1966. Studies on the denaturation of biological macromolecules by chemical carcinogens. I. Aggregation, viscosity and optical rotation changes produced in ovalbumin by nitrosamines and other water-soluble carcinogens. Arzneim. -Forsch. 16: 740-746.

Azum-Gelade, M.C. 1974. Contribution A L'Etude du Mecanisme d'Action Toxique de la Formamide et de ses Derives N-Methyles et N-Ethyles. Thesis. p. 1-134.

Bankowski, O., M. Koethnig and H. Klemt. 1959. Formamide and N-substituted formamides. British Patent 823, 778. Nov. 18, 1959. (CA 54:7563f)

Boublik, T., V. Fried and E. Hala. 1984. The vapor pressures of pure substances: Selected values of the temperature dependence of the vapour pressures of some pure substances in the normal and low pressure region. Vol. 17. Amsterdam, Netherlands.

Cadwallader, D.E. and J.R. Phillips. 1969. Behavior of erythrocytes in various solvent systems. V. Water-liquid amides. J. Pharmacol. Sci. 58: 1220-1224.

Dunlap, W.J., D.C. Shew, J.M. Robertson and C.R. Toussaint. 1976. Organic pollutants contributed to groundwater by a landfill. EPA-600/9-76-004. U.S. EPA, Off. Res. Dev, Ada, OK. p. 96-110.

Eberling, C.L. 1980. Formic acid and derivatives (DMF). In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. 11: 263-267.

Gopal, R. and S.A. Rizvi. 1968. Vapor pressures of some mono- and dialkyl substituted aliphatic amides at different temperatures. J. Ind. Chem. Soc. 45: 13-16.

Grosjean, D., K. Van Cauwenberghe, J. Schmid and J.N. Pitts, Jr. 1978. Formation of nitrosamines and nitramines by photoxidation of amines under a simulated atmospheric conditions. Jt. Conf. Sens. Environ. Pollut. 4: 196-199.

Hine, J. and P.K. Mookerjee. 1975. The intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. J. Org. Chem. 40: 292-298.

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. McGraw-Hill Book Co., New York. p. 15-16.

Mirvish, S.S. and H. Sidransky. 1971. Labeling in vivo of rat liver proteins by tritium-labeled dimethylnitrosamine. Effect of prior treatment with 3-methylcholanthrene, phenobarbitone, dimethylformamide, diethylformamide, aminoacetonitrile, ethionine, and carbon tetrachloride. Biochem. Pharmacol. 20: 3493-3499.

Neely, W.B. 1985. Hydrolysis. In: Environmental Exposure from Chemicals, Volume I, W.B. Neely and G.E. Blau, Ed. CRC Press, Inc., Boca Raton, FL. p. 159.

NTP (National Toxicology Program). 1985. Management Status Report.

Pham, H.C., D.X. Nguyen and M.C. Azum-Gelade. 1971. Toxicological study of formamide and its N-methyl and N-ethyl derivatives. Therapie. 26(3): 409-424.

Pham, H.C., M.C. Azum-Gelade, V.B. Nguyen and D.X. Nguyen. 1972. Effect of formamide and its N-methyl and N-ethyl derivatives on the activity of convulsant and hypnotic drugs. Therapie. 27(5): 873-880.

Sabljic, A. 1984. Prediction of the nature and strength of soil sorption of organic pollutants by molecular topology. J. Agric. Food Chem. 32: 243-246.

Shackelford, W.M. and L.H. Keith. 1976. Frequency of organic compounds identified in water. U.S. EPA, Athens, GA. EPA-600/4-76-062. p. 136.

SRI (Stanford Research Institute). 1985. 1985 Directory of Chemical Producers: United States of America. SRI International, Menlo Park, CA.

U.S. EPA. 1985. Computer printout: Graphic Exposure Modeling System (GEMS) EXAMS model. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1984. Synthetic Organic Chemicals. U.S. Production and Sales, 1983. USITC Publ. 1588, Washington, DC.

Weast, R.C., Ed. 1985. CRC Handbook of Chemistry and Physics, 66th ed. CRC Press, Inc., Boca Raton, FL. p. C-278.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in August, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.